

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization International Bureau



(43) International Publication Date
3 June 2004 (03.06.2004)

PCT

(10) International Publication Number
WO 2004/045608 A1

(51) International Patent Classification⁷: A61K 31/425, 31/427, 9/20

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(21) International Application Number:

PCT/IB2003/005140

(22) International Filing Date:

13 November 2003 (13.11.2003)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

1155/DEL/2002 15 November 2002 (15.11.2002) IN

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(81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States (regional): ARIPO patent (BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— with international search report

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 2004/045608 A1

(54) Title: PHARMACEUTICAL COMPOSITIONS CONTAINING ABIGUANIDE-GLITAZONE COMBINATION

(57) Abstract: The present invention relates to an orally administered pharmaceutical composition that is a combination of two or more antidiabetic agents in which one of the antidiabetic agents is present in an extended release form and the other antidiabetic agent is present in an immediate release form.

PHARMACEUTICAL COMPOSITIONS CONTAINING ABIGUANIDE-GLITAZONE COMBINATION

Field of the Invention

The present invention relates to an orally administered pharmaceutical
5 composition that is a combination of two or more antidiabetic agents in which one of the
antidiabetic agents is present in an extended release form and the other antidiabetic agent
is present in an immediate release form.

Background of the Invention

Diabetes mellitus is a metabolic disorder characterized by hyperglycemia and
10 insulin resistance, and is often associated with other conditions such as obesity,
hypertension, hyperlipidemia, cardiovascular disease, retinopathy, neuropathy, and
nephropathy. The disease is progressive in nature but often can be controlled initially by
diet alone, although it generally requires treatment with drugs, such as sulfonylureas, and
injections of exogenous insulin. Two major forms of diabetes mellitus are now
15 recognized: Type I and Type II. Type I diabetes, or insulin-dependent diabetes, is the
result of an absolute deficiency of insulin, the hormone that regulates glucose utilization;
patients with Type I diabetes are dependent on exogenous insulin for survival. Type II
diabetes, or non-insulin-dependent diabetes (NIDDM), often occurs concurrent with
normal, or even elevated levels of insulin, and appear to be the result of the inability of
20 tissues to respond appropriately to insulin (i.e., insulin resistance). Insulin resistance is a
major susceptibility trait of NIDDM and also is a contributing factor in arteriosclerosis,
hypertension, lipid disorders and polycystic ovarian syndrome.

Conventional treatments for NIDDM have not changed substantially in many
years and have significant limitations. While physical exercise and a reduction in dietary
25 intake of calories can improve the diabetic condition, compliance with this treatment is
generally poor. To increase the plasma level of insulin, physicians sometimes administer
sulfonylureas (e.g., tolbutamide, glipizide). The sulfonylureas stimulate the pancreatic
beta-cells to secrete more insulin. The plasma level of insulin can be directly increased
by injecting insulin after the response to sulfonylureas fails and will result in insulin

concentrations that stimulate even highly insulin-resistant tissues. However, dangerously low levels of plasma glucose can result from these last two treatments, and can theoretically lead to increased insulin resistance due to the even higher plasma insulin levels.

5 Biguanides have been the most widely used class of antidiabetics. They act by increasing insulin activity in peripheral tissues, reducing hepatic glucose output due to inhibition of gluconeogenesis, and reducing the absorption of glucose from the intestine. Metformin, phenformin, buformin, etc. belong to this group. Metformin has been widely prescribed for lowering blood glucose in patients with NIDDM and is marketed in 500,
10 750, 850 and 1000 mg strengths. However, because it is a short acting drug, metformin requires twice-daily or three-times-daily dosing (500 - 850 mg tab 2-3/day or 1000 mg bid with meals). Adverse events associated with metformin include anorexia, nausea,
15 vomiting and diarrhea. The adverse events may be partially avoided by either reducing the initial dose and/or the maintenance dose by taking an extended-release dosage form
rather than a multiple daily doses. Besides reducing the adverse events, administering an
extended-release dosage form provides a reduction in the frequency of administration.

More recently, glitazones have been introduced and are widely used in the treatment of NIDDM. These agents substantially increase insulin sensitivity in muscle, liver, and adipose tissue in several NIDDM animal models, resulting in the correction of
20 elevated plasma levels of glucose, triglycerides and nonesterified fatty acids without the occurrence of hypoglycemia. These agents, also known generically as thiazolidinediones (e.g., troglitazone, rosiglitazone and pioglitazone), function by increasing the sensitivity of peripheral tissues, such as skeletal muscle, towards insulin. Pioglitazone, the most
widely used glitazone, is normally administered at doses from about 15 mg to about
25 45 mg, and is given as a single dose once per day. Another glitazone, rosiglitazone, is administered at doses of about 5 mg to about 10 mg per day.

Biguanides and thiazolidinediones are commercially available in the form of tablets of the individual drugs. The tablets may be in the form of either immediate release (IR) formulations or controlled release (CR) formulations and are administered

orally to patients in need thereof in protocols calling for the single administration of the individual ingredient. Metformin monotherapy is used as a first line treatment in diabetic patients but may be supplemented with other drugs when the secondary failure of the therapy sets in. The addition of a thiazolidinedione agent to concurrent biguanide
5 treatment provides a balance of stimulated release of insulin while ameliorating insulin resistance and thus provides a level of glycemic control unattainable by either medication alone.

Insulin resistance is a common feature characterizing the pathogenesis of Type II diabetes. Metformin improves glucose tolerance but cannot enhance insulin sensitivity.
10 In contrast, glitazones improve glycemic control by improving insulin sensitivity. The glitazones are highly selective and potent agonists for the peroxisome proliferator-activated receptor-gamma (PPAR- γ). Activation of PPAR- γ nuclear receptors regulates the transcription of insulin responsive genes involved in the control of glucose production, transport, and utilization. In addition, PPAR- γ - responsive genes also
15 participate in the regulation of fatty acid metabolism. The antidiabetic activity of glitazones has been demonstrated in those Type II diabetes in which hyperglycemia and/or impaired glucose tolerance is a consequence of insulin resistance in target tissues. A single administration of glitazones activates the insulin receptors for an extended period and may thus be administered as a single dose without there being a need to
20 maintain the plasma concentration.

A combination therapy of a biguanide and a glitazone, therefore, has a synergistic effect on glucose control because both agents act by different but complementary mechanisms. Clinical evaluations have demonstrated the method of treating diabetes by employing combinations of biguanides and glitazones (WO 00/27401 and U.S. Patent
25 No. 6,011,049). Moreover, pharmaceutical compositions having combinations of biguanides and thiazolidinediones and providing controlled or immediate release of both of the drugs are known in the art. For example, U.S. Patent No. 6,296,874 and published U.S. patent application Ser. Nos. 20010036478 A1, 2010034374 A1, and 20010046545 A1 (Adjei et al.) describe controlled release core combinations of a glitazone with a
30 biguanide chosen from metformin, phenformin or buformin in a single dosage form. The

patent applications of Adjei et al. disclose the preparation of such combinations using either silicate polymers or polysaccharides.

U.S. Patent Nos. 6,166,043 and 6,172,090 disclose methods for reducing the amounts and side effects of active components administered to a diabetic patient. One 5 method disclosed includes administering a therapeutically effective amount of an insulin sensitivity enhancer in combination with a biguanide. The insulin sensitivity enhancer in the system is a thiazolidinedione selected from pioglitazone and troglitazone, while the biguanide is selected from metformin, phenformin and buformin. The combination may be administered as an admixture of the agents or the agents administered independently. 10 The thiazolidinedione and the biguanide may be in the form of a conventional immediate release composition.

Although combinations of two antidiabetic agents are known in the art and are convenient to formulate, a combination providing extended release of a water-soluble active ingredient, e.g., a biguanide, and immediate release of a water-insoluble or 15 sparingly soluble active, e.g., a glitazone, is difficult to achieve.

Summary of the Invention

In one general aspect there is provided a solid pharmaceutical dosage form for oral administration. The dosage form includes an extended release layer that includes a biguanide and an immediate release layer that includes a glitazone.

20 Embodiments of the dosage form may include one or more of the following features. For example, the biguanide may be one or more of metformin, phenformin, and buformin. The glitazone may be one or more of pioglitazone, rosiglitazone, troglitazone, ciglitazone and englitazone. After oral administration the biguanide may be released over a period of about 4 to about 36 hours and, more particularly, over a period of about 8 25 to about 24 hours.

The dosage form may be tablets or capsules. The tablet may include a coating. The capsules may include one or more of pellets, beads, granules, multiparticulates, tablets and powder.

The extended release layer may be a matrix and the matrix may have a uniform mixture of the biguanide and one or more rate controlling polymers. The one or more rate-controlling polymers may be hydrophilic polymers, hydrophobic polymers, or a combination thereof. The matrix may further include one or more pharmaceutically acceptable excipients. The pharmaceutically acceptable excipients may be one or more of diluents, lubricants, disintegrants, binders, glidants, coloring and flavoring agents.

5 The biguanide may be layered onto a pharmaceutically inert core or seed. The inert core or seed may be hydrosoluble or hydroinsoluble.

10 The immediate release outer layer may further include film-forming polymers and optionally other pharmaceutically acceptable excipients. The film-forming polymers may be water-soluble polymers. The pharmaceutically acceptable excipients may be one or more of plasticizers, opacifiers and colorants.

15 The dosage form may further include a wetting agent in the immediate release layer such that the immediate release layer includes a glitazone and the wetting agent in a weight ratio ranging from about 10:1 to about 1:25. The wetting agent may be selected from amongst hydrophilic and hydrophobic surfactants. The hydrophilic surfactants may be selected from one or more of non-ionic surfactants, ionic surfactants or mixtures thereof.

20 The hydrophobic surfactants may be selected from one or more of alcohols; polyoxyethylene alkylethers; fatty acids; glycerol fatty acid monoesters; glycerol fatty acid diesters; acetylated glycerol fatty acid monoesters; acetylated glycerol fatty acid diesters, lower alcohol fatty acid esters; polyethylene glycol fatty acid esters; polyethylene glycol glycerol fatty acid esters; polypropylene glycol fatty acid esters; polyoxyethylene glycerides; lactic acid derivatives of monoglycerides; lactic acid 25 derivatives of diglycerides; propylene glycol diglycerides; sorbitan fatty acid esters; polyoxyethylene sorbitan fatty acid esters; polyoxyethylene-polyoxypropylene block copolymers, polyethyleneglycols as esters or ethers, polyethoxylated castor oil; polyethoxylated hydrogenated castor oil, polyethoxylated fatty acid from castor oil or

polyethoxylated fatty acid from castor oil or polyethoxylated fatty acid from hydrogenated castor oil.

The non-ionic surfactants may be selected from one or more of alkylglucosides; alkylmaltosides; alkylthioglucosides; lauryl macrogolglycerides; caprylocaproyl 5 macrogolglycerides, polyoxyethylene alkyl ethers; polyoxyethylene alkylphenols; polyethylene glycol fatty acid esters; polyethylene glycol glycerol fatty acid esters; polyoxyethylene sorbitan fatty acid esters; polyoxyethylene-polyoxypropylene block copolymers; polyglycerol fatty acid esters; polyoxyethylene glycerides; polyoxyethylene sterols, derivatives, and analogues thereof; polyoxyethylene vegetable oils; 10 polyoxyethylene hydrogenated vegetable oils; reaction products of polyols and at least one member of the group consisting of fatty acids, glycerides, vegetable oils, hydrogenated vegetable oils, and sterols; sugar esters, sugar ethers; sucroglycerides; and mixtures thereof.

The ionic surfactants may be selected from one or more of alkyl ammonium salts; 15 bile acids and salts, analogues, and derivatives thereof; fatty acid derivatives of amino acids, oligopeptides, and polypeptides; glyceride derivatives of amino acids, oligopeptides, and polypeptides; acyl lactylates; monoacetylated tartaric acid esters of monoglycerides, monoacetylated tartaric acid esters of diglycerides, diacetylated tartaric acid esters of monoglycerides, diacetylated tartaric acid esters of diglycerides; 20 succinylated monoglycerides; citric acid esters of monoglycerides; citric acid esters of diglycerides; alginate salts; propylene glycol alginate; lecithins and hydrogenated lecithins; lysolecithin and hydrogenated lysolecithins; lysophospholipids and derivatives thereof; phospholipids and derivatives thereof; salts of alkylsulfates; salts of fatty acids; sodium docusate; and mixtures thereof.

25 The extended release layer may be a core and the immediate release layer may cover at least a portion of the core. The dosage form may be a bilayered dosage form. The dosage form may further include one or more of sulfonylurea, insulin, alpha-glucosidase inhibitors, meglitinides, fibrates, statins, squalene synthesis inhibitors and angiotensin-converting enzyme inhibitors.

In another general aspect there is provided a process for preparing a solid, orally administered pharmaceutical dosage form of an extended release core of a biguanide and an immediate release layer of a glitazone. The process includes (a.) dispersing the biguanide in a solid matrix to form a core having a surface; and (b.) layering the
5 immediate release layer of a glitazone on the surface of the core.

Embodiments of the process may include one or more of the following features. For example, layering the immediate release layer may further include layering one or more wetting agents. The glitazone and the one or more wetting agents may be present in the immediate release layer in a weight ratio ranging from about 10:1 to about 1:25. The
10 one or more wetting agents may be selected from amongst hydrophilic or hydrophobic surfactants. The hydrophilic surfactants may be selected from one or more of non-ionic surfactants, ionic surfactants or mixtures thereof.

The hydrophobic surfactants may be selected from one or more of alcohols; polyoxyethylene alkylethers; fatty acids; glycerol fatty acid monoesters; glycerol fatty
15 acid diesters; acetylated glycerol fatty acid monoesters; acetylated glycerol fatty acid diesters, lower alcohol fatty acid esters; polyethylene glycol fatty acid esters; polyethylene glycol glycerol fatty acid esters; polypropylene glycol fatty acid esters; polyoxyethylene glycerides; lactic acid derivatives of monoglycerides; lactic acid derivatives of diglycerides; propylene glycol diglycerides; sorbitan fatty acid esters;
20 polyoxyethylene sorbitan fatty acid esters; polyoxyethylene-polyoxypolypropylene block copolymers, polyethyleneglycols as esters or ethers, polyethoxylated castor oil; polyethoxylated hydrogenated castor oil, polyethoxylated fatty acid from castor oil or polyethoxylated fatty acid from castor oil or polyethoxylated fatty acid from hydrogenated castor oil.

25 The non-ionic surfactants may be selected from one or more of alkylglucosides; alkylmaltosides; alkylthioglucosides; lauryl macrogolglycerides; caprylocaproyl macrogolglycerides, polyoxyethylene alkyl ethers; polyoxyethylene alkylphenols; polyethylene glycol fatty acid esters; polyethylene glycol glycerol fatty acid esters; polyoxyethylene sorbitan fatty acid esters; polyoxyethylene-polyoxypolypropylene block

- copolymers; polyglycerol fatty acid esters; polyoxyethylene glycerides; polyoxyethylene sterols, derivatives, and analogues thereof; polyoxyethylene vegetable oils; polyoxyethylene hydrogenated vegetable oils; reaction products of polyols and at least one member of the group consisting of fatty acids, glycerides, vegetable oils,
- 5 hydrogenated vegetable oils, and sterols; sugar esters, sugar ethers; sucroglycerides; and mixtures thereof.

The ionic surfactants may be selected from amongst alkyl ammonium salts; bile acids and salts, analogues, and derivatives thereof; fatty acid derivatives of amino acids, oligopeptides, and polypeptides; glyceride derivatives of amino acids, oligopeptides, and

10 polypeptides; acyl lactylates; monoacetylated tartaric acid esters of monoglycerides, monoacetylated tartaric acid esters of diglycerides, diacetylated tartaric acid esters of monoglycerides, diacetylated tartaric acid esters of diglycerides; succinylated monoglycerides; citric acid esters of monoglycerides; citric acid esters of diglycerides; alginate salts; propylene glycol alginate; lecithins and hydrogenated lecithins;

15 lysolecithin and hydrogenated lysolecithins; lysophospholipids and derivatives thereof; phospholipids and derivatives thereof; salts of alkylsulfates; salts of fatty acids; sodium docusate; and mixtures thereof.

The biguanide may be selected from one or more of metformin, phenformin and buformin. The glitazone may be selected from one or more of pioglitazone,

20 rosiglitazone, troglitazone, ciglitazone and englitazone. After oral administration the biguanide may be released over a period of about 4 to about 36 hours and, more particularly, over a period of about 8 to about 24 hours.

The process may further include forming a tablet or a capsule. The process may still further include coating the tablet. The capsule may contain one or more of pellets,

25 beads, granules, multiparticulates, tablets and powder.

The core may be a matrix and the matrix may be a uniform mixture of the biguanide and one or more rate controlling polymers. The one or more rate-controlling polymers may be either or both of hydrophilic and hydrophobic. The matrix may further include one or more pharmaceutically acceptable excipients. The pharmaceutically

acceptable excipients may include one or more of diluents, lubricants, disintegrants, binders, glidants, colorants, and flavorants.

The biguanide may be layered onto pharmaceutically inert core or seeds. The inert core or seeds may be hydrosoluble or hydroinsoluble.

5 The immediate release outer layer may further include film-forming polymers and optionally other pharmaceutically acceptable excipients. The film-forming polymers may be water-soluble polymers. The pharmaceutically acceptable excipients may be one or more of plasticizers, opacifiers and colorants.

10 The process may further include placing a seal-coat over the core, the seal-coat including hydrophilic polymers.

In another general aspect there is provided a process for preparing a bilayered, solid, orally administered pharmaceutical dosage form of a biguanide and a glitazone. The process includes (a.) dispersing the biguanide in an extended release carrier base material; (b.) separately dispersing the glitazone in an immediate release carrier base material; and (c.) compressing the material of step a and step b to form bilayered tablet.

15 Embodiments of the process may include one or more of the following features. For example, the immediate release carrier base material may further include one or more wetting agents before or after dispersing the glitazone. The glitazone and the one or more wetting agents may be present in a weight ratio ranging from about 10:1 to about 1:25. 20 The one or more wetting agents may be selected from amongst hydrophilic or hydrophobic surfactants. The hydrophilic surfactants may be selected from one or more of non-ionic surfactants, ionic surfactants or mixtures thereof.

25 The hydrophobic surfactants may be selected from one or more of alcohols; polyoxyethylene alkylethers; fatty acids; glycerol fatty acid monoesters; glycerol fatty acid diesters; acetylated glycerol fatty acid monoesters; acetylated glycerol fatty acid diesters, lower alcohol fatty acid esters; polyethylene glycol fatty acid esters; polyethylene glycol glycerol fatty acid esters; polypropylene glycol fatty acid esters; polyoxyethylene glycerides; lactic acid derivatives of monoglycerides; lactic acid

- derivatives of diglycerides; propylene glycol diglycerides; sorbitan fatty acid esters; polyoxyethylene sorbitan fatty acid esters; polyoxyethylene-polyoxypropylene block copolymers, polyethyleneglycols as esters or ethers, polyethoxylated castor oil; polyethoxylated hydrogenated castor oil, polyethoxylated fatty acid from castor oil or
- 5 polyethoxylated fatty acid from castor oil or polyethoxylated fatty acid from hydrogenated castor oil.

The non-ionic surfactants may be selected from one or more of alkylglucosides; alkylmaltosides; alkylthioglucosides; lauryl macrogolglycerides; caprylocaproyl macrogolglycerides, polyoxyethylene alkyl ethers; polyoxyethylene alkylphenols;

10 polyethylene glycol fatty acid esters; polyethylene glycol glycerol fatty acid esters; polyoxyethylene sorbitan fatty acid esters; polyoxyethylene-polyoxypropylene block copolymers; polyglycerol fatty acid esters; polyoxyethylene glycerides; polyoxyethylene sterols, derivatives, and analogues thereof; polyoxyethylene vegetable oils; polyoxyethylene hydrogenated vegetable oils; reaction products of polyols and at least

15 one member of the group consisting of fatty acids, glycerides, vegetable oils, hydrogenated vegetable oils, and sterols; sugar esters, sugar ethers; sucroglycerides; and mixtures thereof.

The ionic surfactants may be selected from amongst alkyl ammonium salts; bile acids and salts, analogues, and derivatives thereof; fatty acid derivatives of amino acids, oligopeptides, and polypeptides; glyceride derivatives of amino acids, oligopeptides, and polypeptides; acyl lactylates; monoacetylated tartaric acid esters of monoglycerides, monoacetylated tartaric acid esters of diglycerides, diacetylated tartaric acid esters of monoglycerides, diacetylated tartaric acid esters of diglycerides; succinylated monoglycerides; citric acid esters of monoglycerides; citric acid esters of diglycerides;

20 alginate salts; propylene glycol alginate; lecithins and hydrogenated lecithins; lysolecithin and hydrogenated lysolecithins; lysophospholipids and derivatives thereof; phospholipids and derivatives thereof; salts of alkylsulfates; salts of fatty acids; sodium docusate; and mixtures thereof.

The biguanide may be selected from one or more of metformin, phenformin and buformin. The glitazone may be selected from one or more of pioglitazone, rosiglitazone, troglitazone, ciglitazone and englitazone.

After oral administration, the biguanide is released over a period of about 4 to
5 about 36 hours and, more particularly, over a period of about 8 to about 24 hours.

The process may further include forming a tablet or a capsule. The process may still further include coating the tablet. The capsule may contain one or more of pellets, beads, granules, multiparticulates, tablets and powder.

The biguanide layer may be a matrix and the matrix may be a uniform mixture of
10 the biguanide and one or more rate controlling polymers. The one or more rate-controlling polymers may be either or both of hydrophilic polymers and hydrophobic polymers. The matrix may further include one or more pharmaceutically acceptable excipients. The pharmaceutically acceptable excipients may be one or more of diluents, lubricants, disintegrants, binders, glidants, colorants, and flavorants. The biguanide may
15 be layered onto pharmaceutically inert core or seeds. The inert core or seeds may be hydrosoluble or hydroinsoluble.

The immediate release carrier base material may further include one or more film-forming polymers and optionally other pharmaceutically acceptable excipients. The film-forming polymers may be water-soluble polymers. The pharmaceutically acceptable excipients may be one or more of plasticizers, opacifiers and colorants.
20

The process may further include providing a seal-coat of one or more hydrophilic polymers between the two layers.

In another general aspect there is provided a method of treating non-insulin dependent diabetes mellitus in a patient in need thereof. The method includes
25 administering a solid, pharmaceutical dosage form of the combination of a biguanide and a glitazone. The dosage form provides an extended-release of the biguanide and an immediate release of the glitazone.

Embodiments of the method may include one or more of the following features or those described above. For example, the biguanide may be one or more of metformin, phenformin, and buformin and, in particular, may be metformin. The glitazone may be one or more of pioglitazone, rosiglitazone, troglitazone, ciglitazone and englitazone and, 5 in particular, may be pioglitazone.

After oral administration of the dosage form, the biguanide is released over a period of about 4 to about 36 hours and, more particularly, over a period of about 8 to about 24 hours. The dosage form may be tablets or capsules. The dosage form may further include one or more of sulfonylurea, insulin, alpha-glucosidase inhibitors, 10 meglitinides, fibrates, statins, squalene synthesis inhibitors and angiotensin-converting enzyme inhibitors.

The details of one or more embodiments of the inventions are set forth in the description below. Other features, objects and advantages of the inventions will be apparent from the description and claims.

15

Detailed Description of the Invention

Hydrophobic therapeutic agents, i.e., therapeutic compounds having poor solubility in aqueous solution, are difficult to formulate as a dosage form that can be effectively administered to patients. A well-designed formulation must, at a minimum, be capable of presenting a therapeutically effective amount of the hydrophobic compound 20 to the desired absorption site, in an absorbable form. Even this minimal functionality is difficult to achieve when delivery of the hydrophobic therapeutic agent requires interaction with aqueous physiological environments, such as gastric and intestinal fluids. Pharmaceutical compositions for delivering such hydrophobic therapeutic agents must carry the hydrophobic compound through the aqueous environment while both 25 maintaining the hydrophobic compound in an absorbable form and avoiding the use of physiologically harmful solvents or excipients.

A similar problem is faced when formulating extended release dosage forms of highly soluble therapeutic agents. The high solubility of the therapeutic agent requires

the incorporation of a high percentage of the polymer to achieve a desired release profile and prolonged effect. Further, an additional constraint is the necessity of controlling the initial burst of the drug from the formulation.

Therefore, there remains a need for pharmaceutical compositions for oral
5 administration that include a combination of one or more hydrophobic, water-insoluble therapeutic agents, i.e., a glitazone, in immediate release form, and a highly water-soluble therapeutic agent, i.e., a biguanide, in an extended-release form with the characteristics of achieving an effect over 24 hours after once daily administration.

It has now been discovered that a dosage form can be prepared that includes:
10 (a) one layer or a core from which a single highly water-soluble active ingredient is released on a prolonged basis and (b) a coating or layer from which another active ingredient is released on an immediate-release basis. The dosage form provides a high degree of uniformity in the immediate-release portion, even in those circumstances in which the drug in the immediate-release portion is either insoluble or only sparingly
15 soluble in water. This result is achieved by incorporating one or more wetting agents in the immediate release layer in an amount in which the weight ratio of the glitazone to wetting agent ranges from 10:1 to about 1:25.

Specifically, in one aspect there is provided a dosage form that contains both a glitazone and a biguanide. The glitazone is contained in an immediate-release form so
20 that it is released substantially immediately upon ingestion (i.e., upon swallowing). Generally at least 80% of the glitazone is released from the dosage form within an hour after administration. The biguanide, by contrast, releases in a sustained fashion; at least about 75% of the drug contained in the dosage form is released over a period of 4 to 36 hours, preferably about 8 to 24 hours. The term "about" as used above and elsewhere
25 herein means plus or minus 10% for each of the numerical limits.

The pharmaceutical compositions of the present invention can be administered orally in the form of tablets, such as coated-tablets, bilayered tablets or multi-layered tablets, or in form of capsules containing pellets, beads, granules, multiparticulates, tablets or powder.

Biguanide as employed herein is intended to include metformin, phenformin and buformin including their salts, solvates, hydrates and polymorphs. Particularly, the biguanide used may be metformin. Different salts of metformin that can be used include hydrochloride, acetate, maleate, fumarate, succinate and other salts. The daily effective 5 dose of metformin may range from about 500 mg to about 2550 mg, and, in particular, the dose may be a single dose of about 500 mg to about 1000 mg. The biguanide is present in an amount from about 40% to about 75% by weight of the total composition.

The biguanide may be incorporated in an extended release carrier base by dispersing the biguanide in a rate-controlling polymer matrix, as described in our pending 10 application, published as WO 03/028704. Alternatively, the biguanide may be layered onto pharmaceutically acceptable inert cores or seeds in admixture with rate-controlling polymers or surrounded by rate-controlling polymers.

The term matrix, as used herein, refers to a uniform mixture of a biguanide, rate-controlling polymers, and, optionally, other pharmaceutically acceptable excipients. The 15 rate-controlling polymers may be hydrophilic, hydrophobic or a combination thereof. The rate-controlling polymers are uniformly dispersed throughout the matrix to achieve uniform drug release. Hydrophilic polymers of the present invention include, for example, cellulose derivatives such as hydroxypropylcellulose, hydroxypropyl methylcellulose, hydroxyethylcellulose, hydroxymethylcellulose, carboxymethylcellulose, methylcellulose, sodium carboxymethylcellulose or combinations thereof. The hydrophobic polymers include one or more of poly (ethylene) oxide, ethyl cellulose, cellulose acetate, cellulose acetate butyrate, hydroxypropyl methylcellulose phthalate, poly (alkyl) methacrylate, copolymers of acrylic or methacrylic acid esters, waxes, shellac, and hydrogenated vegetable oils.

20 In addition to the one or more active ingredients and rate-controlling polymers, the matrix may contain other pharmaceutically acceptable excipients that act in one or more capacities as diluents, binders, lubricants, glidants, colorants or flavoring agents.

Suitable diluents include pharmaceutically acceptable inert fillers such as microcrystalline cellulose, lactose, dibasic calcium phosphate, mannitol, starch, sorbitol, sucrose, dextrose, maltodextrin or mixtures thereof.

5 Suitable binders include one or more of polyvinyl pyrrolidone, lactose, starches, gums, waxes, gelatin, polymers or mixtures thereof.

Suitable lubricants include one or more of colloidal silicon dioxide, talc, stearic acid, magnesium stearate, magnesium silicate, polyethylene, sodium benzoate, sodium lauryl sulphate, fumaric acid, zinc stearate, paraffin, or mixtures thereof.

Suitable glidants include one or more of talc and colloidal silicon dioxide.

10 The matrix may be made by any pharmaceutically acceptable technique that achieves uniform blending, e.g., dry blending, dry granulation, wet granulation, compaction, and fluid bed granulation.

15 The matrix formed can be compressed to form the tablets. Alternatively, the matrix may be formulated as a plurality of discrete or aggregated particles, pellets, beads or granules.

As described above, the biguanide may be layered onto cores or seeds. The inert core or seeds may be hydro soluble, such as sucrose, lactose, maltodextrin and the like, or hydro insoluble, such as microcrystalline cellulose, partially pregelatinized starch, dicalcium phosphate and the like. The biguanide and the rate controlling polymer can be 20 coated as single layer or as separate layers on these inert cores, granulated with the inert cores, or mixed with the inert cores and extruded and spheronized to form the pellets.

The coating may be applied to the inert/active core using a conventional coating pan, a spray coater, a rotating perforated pan, or an automated system, such as a centrifugal fluidizing (CF) granulator, a fluidized bed process, or any other suitably 25 automated coating equipment.

The extended-release core containing a biguanide may optionally be coated to seal the core. The coated active cores may be dried under conditions effective for drying, e.g., in an oven or by means of gas in a fluidized bed.

Finally, these beads/pellets may be filled into capsules or compressed to form the tablets. The capsule dosage form may include a plurality of pellets, granules or beads or a single compressed tablet which release the biguanide over an extended period of time.

Glitazone as employed herein is intended to include, but is not limited to, pioglitazone, rosiglitazone, troglitazone, ciglitazone, englitazone, and their salts, solvates, hydrates and polymorphs. In particular, the glitazone may be pioglitazone. The daily effective dose of pioglitazone may range from 5 mg to 50 mg and, in particular, the dose may be a single dose of 10 mg to 45 mg. The glitazone may be present in an amount of from about 0.5% to about 10% by weight of the total composition.

A glitazone can be incorporated into the dosage form as an immediate release component in a variety of ways. For example, it can be incorporated into an exterior coating of a tablet from which it releases substantially immediately upon ingestion. Such a coating can similarly be applied to each of the particles that make up a multiparticulate system, i.e., granules, beads. If the dosage form is to be a capsule, the glitazone can be contained in a single pellet inside the capsule from which it releases substantially immediately once the capsule shell dissolves. Alternatively, the glitazone can be contained in several smaller pellets, can be present as one or more immediate release particles, or can be present as one or more immediate release layers over the extended release cores or beads. Any conventional method may be used for the preparation of the layer of the glitazone. Conventional pharmaceutically acceptable excipients may be incorporated into this layer. These excipients may include diluents, binders and lubricants.

The coating composition for coating the glitazone may include water-soluble polymers such as polyvinyl pyrrolidone, hydroxypropyl cellulose, polyvinyl alcohol, hydroxypropyl methylcellulose and the like. The polymer may be applied as a solution in an organic solvent or as an aqueous dispersion. The solvent may be, for example, one or

more of water; alcohol such as ethyl alcohol or isopropyl alcohol; ketones such as acetone or ethylmethyl ketone; and chlorinated hydrocarbons such as dichloroethane and trichloroethane. The coating composition may also include plasticizers, opacifiers and colorants. Any conventional coating equipment may be employed to facilitate coating,
5 including a centrifugal fluidized bed coating apparatus, pan coating apparatus, or fluidized bed granulating coating apparatus.

Due to poor dispersibility in solvents, the film-coating composition that includes the glitazone may optionally include a wetting agent. Suitable wetting agents include hydrophilic and hydrophobic surfactants. Hydrophilic surfactants may be selected from
10 one or more of hydrophilic non-ionic surfactants, hydrophilic ionic surfactants, and combinations thereof.

Non-ionic surfactants may be selected from one or more of alkylglucosides; alkylmaltosides; alkylthioglucosides; lauryl macrogolglycerides; caprylocaproyl macrogolglycerides, polyoxyethylene alkyl ethers; polyoxyethylene alkylphenols;
15 polyethylene glycol fatty acid esters; polyethylene glycol glycerol fatty acid esters; polyoxyethylene sorbitan fatty acid esters; polyoxyethylene-polyoxypropylene block copolymers; polyglycerol fatty acid esters; polyoxyethylene glycerides; polyoxyethylene sterols, derivatives, and analogues thereof; polyoxyethylene vegetable oils; polyoxyethylene hydrogenated vegetable oils; reaction products of polyols and at least
20 one member of the group consisting of fatty acids, glycerides, vegetable oils, hydrogenated vegetable oils, and sterols; sugar esters, sugar ethers; sucroglycerides; and mixtures thereof.

Ionic surfactants may be selected from one or more of alkyl ammonium salts; bile acids and salts, analogues, and derivatives thereof; fatty acid derivatives of amino acids,
25 oligopeptides, and polypeptides; glyceride derivatives of amino acids, oligopeptides, and polypeptides; acyl lactylates; monoacetylated tartaric acid esters of monoglycerides, monoacetylated tartaric acid esters of diglycerides, diacetylated tartaric acid esters of monoglycerides, diacetylated tartaric acid esters of diglycerides; succinylated monoglycerides; citric acid esters of monoglycerides; citric acid esters of diglycerides;

alginate salts; propylene glycol alginate; lecithins and hydrogenated lecithins; lysolecithin and hydrogenated lysolecithins; lysophospholipids and derivatives thereof; phospholipids and derivatives thereof; salts of alkylsulfates; salts of fatty acids; sodium docusate; and mixtures thereof.

5 Hydrophobic surfactants may be selected from one or more of alcohols; polyoxyethylene alkylethers; fatty acids; glycerol fatty acid monoesters; glycerol fatty acid diesters; acetylated glycerol fatty acid monoesters; acetylated glycerol fatty acid diesters, lower alcohol fatty acid esters; polyethylene glycol fatty acid esters; polyethylene glycol glycerol fatty acid esters; polypropylene glycol fatty acid esters; 10 polyoxyethylene glycerides; lactic acid derivatives of monoglycerides; lactic acid derivatives of diglycerides; propylene glycol diglycerides; sorbitan fatty acid esters; polyoxyethylene sorbitan fatty acid esters; polyoxyethylene-polyoxypropylene block copolymers, polyethyleneglycols as esters or ethers, polyethoxylated castor oil; polyethoxylated hydrogenated castor oil, polyethoxylated fatty acid from castor oil or 15 polyethoxylated fatty acid from castor oil or polyethoxylated fatty acid from hydrogenated castor oil.

The glitazone and the wetting agent may be present in a weight ratio ranging from about 10:1 to about 1:25.

20 Of one of the embodiments, there is provided a bilayered dosage form for the combination of a biguanide and a glitazone. The term 'bilayered' as used herein is meant to encompass solid dosage forms in which there are two separate drug layers, with only one surface in contact with each other. These may be prepared, for example, by compressing additional granulation on a previously compressed granulation or alternatively by feeding previously compressed tablets into a machine and compressing 25 another granulation layer around the preformed tablets.

An example of a bi-layer tablet manufacturing method includes: (1) blending a quantity of a glitazone with various excipients, colorants, and/or other pharmaceutically acceptable excipients and additives to form an immediate release formulation, (2) blending a quantity of a biguanide with a rate-controlling polymer, and various

excipients, colorants, and/or other pharmaceutical additives to form an extended release formulation, and (3) compressing a quantity of the immediate release formulation of the glitazone with a quantity of the extended release formulation of the biguanide to form a bi-layer tablet.

5 One of the embodiments includes providing a seal coat of hydrophilic polymers between the extended-release and immediate-release layers.

Other embodiments include modifications relating to coating the tablet with the polymer in order to modify the release of the drug. The solid dosage forms may be optionally coated with non-functional coatings well known in the art, or with coatings
10 that further modify the release of the drug from the dosage form. All such modifications as may be done and understood by those who are skilled in the art are within the scope of the present invention. For example, one such modification includes making the composition into a layered tablet in which the composition provides extended release of more than one therapeutic agent, or extended release of one of the therapeutic agents and
15 immediate or delayed release of the other therapeutic agent(s).

EXAMPLE 1

	INGREDIENTS	Mg/tablet
<u>CORE</u>	Metformin Hydrochloride	500
	Microcrystalline Cellulose	245
	Sodium Carboxymethyl Cellulose	150
	Purified Water	q.s.
	Hydroxypropyl methylcellulose	100
	Magnesium Stearate	5
<u>SEAL COAT</u>	Hydroxypropyl methylcellulose E5	15.6
	Polyethylene glycol 4000	4.8
	Titanium Dioxide	2.4
	Talc	1.2
	Purified Water	q.s.
<u>ACTIVE COAT</u>	Pioglitazone Hydrochloride equivalent to Pioglitazone (30 mg)	39.672
	Caprylocaproyl Macrogolglycerides	18
	Hydroxypropyl methylcellulose E5	40.3
	Polyethylene glycol 4000	12.4
	Titanium Dioxide	6.2
	Talc	3.1
	Purified Water	q.s.

Procedure:

1. Metformin hydrochloride was milled through a 1 mm screen and mixed with microcrystalline cellulose and sodium carboxymethyl cellulose. The blend was sieved through a No. 44 mesh, transferred to a rapid mixer granulator, and wet granulated with purified water. The granules were dried in a fluid bed dryer, sized through a multimill, and sifted through a No. 30 mesh.
- 5

2. Hydroxypropyl methylcellulose was separately sifted through a No. 30 mesh and mixed with the granules of step 1 in a low shear mixer. The blend was then mixed with magnesium stearate and compressed into tablets.
3. A coating dispersion was prepared by dispersing all of the ingredients of the seal coat in water. The tablets were coated with this dispersion until a weight build up of 2% was achieved.
5
4. To prepare the active coat, caprylocaproyl monoglyceride was dissolved in purified water. To this solution, pioglitazone hydrochloride was added with stirring to form a dispersion. The other ingredients of the active coat were added with stirring to this dispersion and the resulting dispersion was then spray coated upon the tablets obtained from step 3 until a weight build up of 10% was
10 achieved.

EXAMPLE 2

	INGREDIENTS	Mg/tablet
<u>CORE</u>	Metformin Hydrochloride	500
	Microcrystalline Cellulose	245
	Sodium Carboxymethyl Cellulose	150
	Hydroxypropyl methylcellulose	100
	Magnesium Stearate	5
<u>SEAL COAT</u>	Hydroxypropyl methylcellulose E5	15.6
	Polyethylene glycol 4000	4.8
	Titanium Dioxide	2.4
	Talc	1.2
	Purified Water	q.s.
<u>ACTIVE COAT</u>	Pioglitazone Hydrochloride equivalent to Pioglitazone (30 mg)	39.672
	Hydroxypropyl methylcellulose E5	37.2
	Polyethylene glycol 400	7.2
	Titanium Dioxide	6.2
	Talc	12.0
	Methylene chloride	q.s.
	Isopropyl alcohol	q.s.

Procedure:

1. Metformin hydrochloride was milled through a 1 mm screen and mixed with microcrystalline cellulose and sodium carboxymethyl cellulose. The blend was sieved through a No. 44 mesh.
2. Hydroxypropyl methylcellulose was separately sifted through a No. 30 mesh and mixed with the blend of step 1 in a low shear mixer. The blend was then mixed with magnesium stearate compressed into tablets.
3. A coating dispersion was prepared by dispersing all of the ingredients of the seal coat in water. The tablets were coated with this dispersion until a weight build up of 2% was achieved.

4. To prepare the active coat, pioglitazone hydrochloride was dissolved in a methylene chloride and isopropyl alcohol mix (ratio of 2:1). The other ingredients of the active coat then were added with stirring to this solution and the resulting dispersion was spray coated upon the tablets obtained from step 3 until a weight build up of 10% was achieved.
- 5

EXAMPLE 3

	INGREDIENTS	Mg/tablet
<u>CORE</u>	Metformin Hydrochloride	500
	Microcrystalline Cellulose	245
	Sodium Carboxymethyl Cellulose	150
	Hydroxypropyl methylcellulose	100
	Magnesium Stearate	5
<u>SEAL COAT</u>	Hydroxypropyl methylcellulose E5	15.6
	Polyethylene glycol 4000	4.8
	Titanium Dioxide	2.4
	Talc	1.2
	Purified Water	q.s.
<u>ACTIVE COAT</u>	Pioglitazone Hydrochloride equivalent to Pioglitazone (15 mg)	19.836
	Caprylocaporyl Macrogolglycerides	14.4
	Hydroxypropyl methylcellulose E5	40.3
	Polyethylene glycol 4000	12.4
	Titanium Dioxide	6.2
	Talc	3.1
	Purified Water	q.s.

Procedure:

1. Metformin hydrochloride was milled through a 1 mm screen and mixed with microcrystalline cellulose and sodium carboxymethyl cellulose. The blend was sieved through a No. 44 mesh.
- 10

2. Hydroxypropyl methylcellulose was separately sifted through a No. 30 mesh and mixed with the blend of step 1 in a low shear mixer. The blend was then mixed with magnesium stearate, passed through a roller compactor, and milled again to form granules. These granules were then compressed into tablets.
- 5 3. A coating dispersion was prepared by dispersing all of the ingredients of the seal coat in water. The tablets were coated with this dispersion until a weight build up of 2% was achieved.
- 10 4. To prepare the active coat, caprylocaproyl monoglyceride was dissolved in purified water. To this solution, pioglitazone hydrochloride was added with stirring to form dispersion. The other ingredients of the active coat were added with stirring to this dispersion and the resulting dispersion was spray coated upon the tablets obtained from step 3 until the weight build up of 8.0% was achieved.

15 A comparative dissolution profile of metformin hydrochloride in the innovator's marketed tablets (Glucophage XR 500 mg) and tablet formulation made in accordance with the invention disclosed in Example 3 was obtained. The dissolution was carried out in USP Apparatus Type I (basket) at a speed of 100 rpm. The medium was 900 ml phosphate buffer pH 6.8. The data obtained is disclosed in Table 1.

Table 1. Comparative dissolution profile of metformin hydrochloride in Glucophage XR 500 mg versus the tablets of Example 3

Time (hrs)	Percent (%) Metformin hydrochloride released	
	Glucophage XR	Tablets (Example 3)
0	0	0
1	29	28
2	41	43
4	60	65
8	83	92
10	90	100
12	99	101

From the results, it is evident that approximately all the drug is released in twelve hours in both formulations thereby showing substantially similar dissolution profiles.

A comparative dissolution profile of pioglitazone hydrochloride in the innovator's marketed tablets (Actos, 15 mg) and tablet formulation made in accordance with

- 5 Example 3 was obtained. The dissolution was carried out in USP Apparatus Type I at a speed of 100 rpm. The medium was 900 ml 0.1 N hydrochloric acid. The data obtained is disclosed in Table 2.

Table 2. Comparative dissolution profile of pioglitazone hydrochloride in Actos 15 mg versus tablets of Example 3

Time (hrs)	Percent (%) Pioglitazone hydrochloride released	
	Actos 15 mg	Tablets (Example 3)
0	0	0
15	100	95
30	101	104
45	101	106

- 10 From the results, it is evident that more than 95% of the drug is released in 15 minutes in both formulations thereby showing substantially similar dissolution profiles.

Pharmacokinetics

The drug release was evaluated in vivo in a randomized, two treatment, two period, single dose, crossover bioavailability study. The study was conducted in twelve 15 healthy, adult, male, human subjects under fasting conditions. A single OD dose of pioglitazone hydrochloride and 500 mg metformin hydrochloride was administered after an overnight fasting of 10 hours with 240 ml of 20% glucose water. The OD dosage was compared to pioglitazone tablets 15 mg (Actos manufactured by Takeda Pharmaceuticals, USA) and metformin extended release 500mg tablets (Glucophage XR tablets 20 manufactured by Bristol-Myers Squibb, USA). There was a washout period of seven days. All subjects were on fast overnight for a period of 10 hours before commencement

of dosing. Drinking water was not allowed from one hour pre-dosing to 10 hour post dosing. Uniform and low fat meals were provided to all the subjects.

The plasma pioglitazone and metformin concentrations were measured by high performance liquid chromatographic (HPLC) method using an ultraviolet (UV) detector.

- 5 The results are provided below.

Pioglitazone: The OD formulation showed a T_{max} of 2.9 ± 0.1287 as compared to a T_{max} of 3.02 ± 0.3608 for the reference formulation, indicating that the test and reference formulations have substantially the same mean values.

The OD formulation gave a serum concentration time profile similar to the 10 reference formulation. The peak serum concentration (C_{max}) was comparable to that for the reference formulation, indicating a similar rate of absorption of pioglitazone. The total bioavailability of pioglitazone measured as area under the curve ($AUC 0-\infty$) was also comparable to that of the reference tablets, indicating that the entire drug was released from the formulation and absorbed during its transit through gastrointestinal 15 tract. These results are presented in Table 3.

Table 3. Piaglitazone Pharmacokinetic Data

Parameters	Reference	Test
C_{max} (ng/ml)	743.588 ± 67.44	727.724 ± 118.21
T_{max} (hr)	3.02 ± 0.3608	2.90 ± 0.1287
$AUC (0-\infty)$ ng/ml.hr)	5835.98 ± 1284.71	5554.94 ± 1232.29

Further, referring to Table 4, the extent of absorption for the test product was comparable to that for the reference product as indicated by the ratio of test to reference (T/R ratio). The 90% confidence intervals were found to be within the bioequivalence 20 acceptance range of 80-120% for the untransformed data (as per Drug Controller General of India (DCGI) draft guidelines). The results are shown in Table 4.

Table 4. 90% Confidence Intervals for Pioglitazone Pharmacokinetic data

Parameters	Ratio (%) (Test/Reference)	90% Confidence Intervals
Cmax (ng/ml)	97.75	90.97 - 104.53
Aug (0- ∞) (ng/ml.hr)	94.79	86.92 - 102.66

Metformin: The OD formulation showed a Tmax of 3.88 ± 0.8013 as compared to 3.58 ± 0.8940 of reference formulation, indicating that test and reference formulations have nearly same mean values.

5 Referring to Table 5, the OD formulation made in accordance with Example 3 gave a serum concentration time profile similar to the reference formulation. The peak serum concentration (Cmax) was comparable to that for the reference formulation, indicating a similar rate of absorption of metformin hydrochloride. The total bioavailability of metformin measured as the area under the curve (AUC 0- ∞) was also
10 comparable to that of the reference tablets, indicating that the entire drug was released from the formulation and absorbed during its transit through gastrointestinal tract.

Table 5. Metformin Pharmacokinetic Data

Parameters	Reference	Test
Cmax (ng/ml)	633.227 ± 109.33	670.527 ± 116.392
Tmax (hr)	3.02 ± 0.3608	3.58 ± 0.8940
AUC (0- ∞) ng/ml.hr)	4653.866 ± 1463.9	4380.234 ± 1110.44

Further, referring to Table 6, the extent of absorption for the test product was comparable to that for the reference product as indicated by the ratio of test to reference
15 (T/R ratio). The 90% confidence intervals were found to be within the bioequivalence acceptance range of 80-120% for the untransformed data (as per DCG1 draft guidelines).

Table 6. 90% Confidence Intervals for Metformin Pharmacokinetic data

Parameters	Ratio (%) (Test/Reference)	90% Confidence Intervals
Cmax (ng/ml)	107.24	96.23 - 118.25
Aug (0-∞) (ng/ml.hr)	96.43	84.07 - 108.79

While several particular forms of the invention have been illustrated and described, it will be apparent that various modifications and combinations of the invention detailed in the text can be made without departing from the spirit and scope of the invention. For example, a bilayered tablet comprising an extended-release biguanide in one layer and an immediate-release glitazone in another layer may be prepared of the example given below.

EXAMPLE 4

Preparation of bilayered tablets:

	INGREDIENTS	Mg/tablet
<u>Metformin layer</u>	Metformin Hydrochloride	500
	Microcrystalline Cellulose	245
	Sodium Carboxymethyl Cellulose	150
	Hydroxypropyl methylcellulose	100
	Magnesium Stearate	5
<u>Seal Coat</u>	Hydroxypropyl methylcellulose E5	15.6
	Polyethylene glycol 4000	4.8
	Titanium Dioxide	2.4
	Talc	1.2
<u>Pioglitazone layer</u>	Pioglitazone hydrochloride equiv. to pioglitazone (30 mg)	39.672
	Lactose	80
	Hydroxypropyl cellulose	2.4
	Carboxymethyl cellulose calcium	3.6
	Magnesium stearate	1.2
	Purified water	q.s.

Procedure:

1. Metformin hydrochloride was milled and mixed with microcrystalline cellulose and sodium carboxymethyl cellulose. The blend was sieved.
- 5 2. Hydroxypropyl methylcellulose was separately sifted and mixed with the blend of step 1 in a low shear mixer. The blend was then mixed with magnesium stearate and passed through roller compactor and then milled again to form granules.
3. Pioglitazone, lactose, hydroxypropyl cellulose and carboxymethylcellulose calcium were blended and granulated with purified water.
4. The wet mass of step 3 was granulated, dried and sifted.
- 10 5. The lubricated granules of metformin and pioglitazone were compressed into bilayer tablets using a rotary compression machine.

Further, it is contemplated that any single feature or any combination of optional features of the inventive variations described herein may be specifically excluded from the claimed invention and be so described as a negative limitation. Accordingly, it is not 15 intended that the invention be limited, except as by the appended claims.

We Claim:

- 1 1. A solid pharmaceutical dosage form for oral administration, the dosage form
2 comprising:
3 an extended release layer comprising a biguanide; and
4 an immediate release layer comprising a glitazone.
- 1 2. The dosage form of claim 1, wherein the biguanide comprises one or more of
2 metformin, phenformin, and buformin.
- 1 3. The dosage form of claim 1, wherein the biguanide is metformin.
- 1 4. The dosage form of claim 1, wherein the glitazone comprises one or more of
2 pioglitazone, rosiglitazone, troglitazone, ciglitazone and englitazone.
- 1 5. The dosage form of claim 4, wherein the glitazone is pioglitazone.
- 1 6. The dosage form of claim 1, wherein after oral administration the biguanide is
2 released over a period of about 4 to about 36 hours.
- 1 7. The dosage form of claim 6, wherein the biguanide is released over a period of
2 about 8 to about 24 hours.
- 1 8. The dosage form of claim 1, wherein the dosage form comprises tablets or
2 capsules.
- 1 9. The dosage form of claim 8, wherein the tablet includes a coating.
- 1 10. The dosage form of claim 8, wherein the capsules include one or more of pellets,
2 beads, granules, multiparticulates, tablets and powder.
- 1 11. The dosage form of claim 1, wherein the extended release layer comprises a
2 matrix.
- 1 12. The dosage form of claim 11, wherein the matrix comprises a uniform mixture of
2 the biguanide and one or more rate controlling polymers.

- 1 13. The dosage form of claim 12, wherein the one or more rate-controlling polymers
2 comprises hydrophilic polymers, hydrophobic polymers, or a combination
3 thereof.
- 1 14. The dosage form of claim 11, wherein the matrix further comprises one or more
2 pharmaceutically acceptable excipients.
- 1 15. The dosage form of claim 14, wherein the pharmaceutically acceptable excipients
2 comprise one or more of diluents, lubricants, disintegrants, binders, glidants,
3 coloring and flavoring agents.
- 1 16. The dosage form of claim 1, wherein the biguanide is layered onto a
2 pharmaceutically inert core or seed.
- 1 17. The dosage form of claim 16, wherein the inert core or seed is hydrosoluble or
2 hydroinsoluble.
- 1 18. The dosage form of claim 1, wherein the immediate release outer layer further
2 comprises film-forming polymers and optionally other pharmaceutically
3 acceptable excipients.
- 1 19. The dosage form of claim 18, wherein the film-forming polymers are water-
2 soluble polymers.
- 1 20. The dosage form of claim 18, wherein the pharmaceutically acceptable excipients
2 comprises one or more of plasticizers, opacifiers and colorants.
- 1 21. The dosage form of claim 1, further comprising one or more of sulfonylurea,
2 insulin, alpha-glucosidase inhibitors, meglitinides, fibrates, statins, squalene
3 synthesis inhibitors and angiotensin-converting enzyme inhibitors.
- 1 22. The dosage form of claim 1, further comprising a wetting agent in the immediate
2 release layer, wherein the immediate release layer comprises the glitazone and the
3 wetting agent in a weight ratio ranging from about 10:1 to about 1:25.

- 1 23. The dosage form of claim 22, wherein the wetting agent is selected from amongst
2 hydrophilic and hydrophobic surfactants.
- 1 24. The dosage form of claim 23, wherein the hydrophilic surfactants are selected
2 from one or more of non-ionic surfactants, ionic surfactants or mixtures thereof.
- 1 25. The dosage form of claim 23, wherein the hydrophobic surfactants are selected
2 from one or more of alcohols; polyoxyethylene alkylethers; fatty acids; glycerol
3 fatty acid monoesters; glycerol fatty acid diesters; acetylated glycerol fatty acid.
4 monoesters; acetylated glycerol fatty acid diesters, lower alcohol fatty acid esters;
5 polyethylene glycol fatty acid esters; polyethylene glycol glycerol fatty acid
6 esters; polypropylene glycol fatty acid esters; polyoxyethylene glycerides; lactic
7 acid derivatives of monoglycerides; lactic acid derivatives of diglycerides;
8 propylene glycol diglycerides; sorbitan fatty acid esters; polyoxyethylene sorbitan
9 fatty acid esters; polyoxyethylene-polyoxypropylene block copolymers,
10 polyethyleneglycols as esters or ethers, polyethoxylated castor oil;
11 polyethoxylated hydrogenated castor oil, polyethoxylated fatty acid from castor
12 oil or polyethoxylated fatty acid from castor oil or polyethoxylated fatty acid from
13 hydrogenated castor oil.
- 1 26. The dosage form of claim 24, wherein the non-ionic surfactants are selected from
2 one or more of alkylglucosides; alkylmaltosides; alkylthioglucosides; lauryl
3 macrogolglycerides; caprylocaproyl macrogolglycerides, polyoxyethylene alkyl
4 ethers; polyoxyethylene alkylphenols; polyethylene glycol fatty acid esters;
5 polyethylene glycol glycerol fatty acid esters; polyoxyethylene sorbitan fatty acid
6 esters; polyoxyethylene-polyoxypropylene block copolymers; polyglycerol fatty
7 acid esters; polyoxyethylene glycerides; polyoxyethylene sterols, derivatives, and
8 analogues thereof; polyoxyethylene vegetable oils; polyoxyethylene hydrogenated
9 vegetable oils; reaction products of polyols and at least one member of the group
10 consisting of fatty acids, glycerides, vegetable oils, hydrogenated vegetable oils,
11 and sterols; sugar esters, sugar ethers; sucroglycerides; and mixtures thereof.

- 1 27. The dosage form of claim 24, wherein the ionic surfactants are selected from one
- 2 or more of alkyl ammonium salts; bile acids and salts, analogues, and derivatives
- 3 thereof; fatty acid derivatives of amino acids, oligopeptides, and polypeptides;
- 4 glyceride derivatives of amino acids, oligopeptides, and polypeptides; acyl
- 5 lactylates; monoacetylated tartaric acid esters of monoglycerides, monoacetylated
- 6 tartaric acid esters of diglycerides, diacetylated tartaric acid esters of
- 7 monoglycerides, diacetylated tartaric acid esters of diglycerides; succinylated
- 8 monoglycerides; citric acid esters of monoglycerides; citric acid esters of
- 9 diglycerides; alginate salts; propylene glycol alginate; lecithins and hydrogenated
- 10 lecithins; lysolecithin and hydrogenated lysolecithins; lysophospholipids and
- 11 derivatives thereof; phospholipids and derivatives thereof; salts of alkylsulfates;
- 12 salts of fatty acids; sodium docusate; and mixtures thereof.
- 1 28. The dosage form of claim 1, wherein the extended release layer comprises a core
- 2 and the immediate release layer covers at least a portion of the core.
- 1 29. The dosage form of claim 1, wherein the dosage form comprises a bilayered
- 2 dosage form.
- 1 30. A process for preparing a solid, orally administered pharmaceutical dosage form
- 2 of an extended release core of a biguanide and an immediate release layer of a
- 3 glitazone, the process comprising:
 - 4 a. dispersing the biguanide in a solid matrix to form a core having a surface; and
 - 5 b. layering the immediate release layer of the glitazone on the surface of the
 - 6 core.
- 1 31. The process of claim 30, wherein layering the immediate release layer further
- 2 comprises layering one or more wetting agents.
- 1 32. The process of claim 31, wherein the glitazone and the one or more wetting
- 2 agents are present in the immediate release layer in a weight ratio ranging from
- 3 about 10:1 to about 1:25.

- 1 33. The process of claim 31, wherein the one or more wetting agents are selected
2 from amongst hydrophilic or hydrophobic surfactants.
- 1 34. The process of claim 33, wherein the hydrophilic surfactants are selected from
2 one or more of non-ionic surfactants, ionic surfactants or mixtures thereof.
- 1 35. The process of claim 33, wherein the hydrophobic surfactants are selected from
2 one or more of alcohols; polyoxyethylene alkylethers; fatty acids; glycerol fatty
3 acid monoesters; glycerol fatty acid diesters; acetylated glycerol fatty acid
4 monoesters; acetylated glycerol fatty acid diesters, lower alcohol fatty acid esters;
5 polyethylene glycol fatty acid esters; polyethylene glycol glycerol fatty acid
6 esters; polypropylene glycol fatty acid esters; polyoxyethylene glycerides; lactic
7 acid derivatives of monoglycerides; lactic acid derivatives of diglycerides;
8 propylene glycol diglycerides; sorbitan fatty acid esters; polyoxyethylene sorbitan
9 fatty acid esters; polyoxyethylene-polyoxypropylene block copolymers,
10 polyethyleneglycols as esters or ethers, polyethoxylated castor oil;
11 polyethoxylated hydrogenated castor oil, polyethoxylated fatty acid from castor
12 oil or polyethoxylated fatty acid from castor oil or polyethoxylated fatty acid from
13 hydrogenated castor oil.
- 1 36. The process of claim 34, wherein the non-ionic surfactants are selected from one
2 or more of alkylglucosides; alkylmaltosides; alkylthioglucosides; lauryl
3 macrogolglycerides; caprylocaproyl macrogolglycerides, polyoxyethylene alkyl
4 ethers; polyoxyethylene alkylphenols; polyethylene glycol fatty acid esters;
5 polyethylene glycol glycerol fatty acid esters; polyoxyethylene sorbitan fatty acid
6 esters; polyoxyethylene-polyoxypropylene block copolymers; polyglycerol fatty
7 acid esters; polyoxyethylene glycerides; polyoxyethylene sterols, derivatives, and
8 analogues thereof; polyoxyethylene vegetable oils; polyoxyethylene hydrogenated
9 vegetable oils; reaction products of polyols and at least one member of the group
10 consisting of fatty acids, glycerides, vegetable oils, hydrogenated vegetable oils,
11 and sterols; sugar esters, sugar ethers; sucroglycerides; and mixtures thereof.

- 1 37. The process of claim 34, wherein the ionic surfactants are selected from one or
2 more of alkyl ammonium salts; bile acids and salts, analogues, and derivatives
3 thereof; fatty acid derivatives of amino acids, oligopeptides, and polypeptides;
4 glyceride derivatives of amino acids, oligopeptides, and polypeptides; acyl
5 lactylates; monoacetylated tartaric acid esters of monoglycerides, monoacetylated
6 tartaric acid esters of diglycerides, diacetylated tartaric acid esters of
7 monoglycerides, diacetylated tartaric acid esters of diglycerides; succinylated
8 monoglycerides; citric acid esters of monoglycerides; citric acid esters of
9 diglycerides; alginate salts; propylene glycol alginate; lecithins and hydrogenated
10 lecithins; lysolecithin and hydrogenated lysolecithins; lysophospholipids and
11 derivatives thereof; phospholipids and derivatives thereof; salts of alkylsulfates;
12 salts of fatty acids; sodium docusate; and mixtures thereof.
- 1 38. The process of claim 30, wherein the biguanide is selected from one or more of
2 metformin, phenformin and buformin.
- 1 39. The process of claim 30, wherein the biguanide comprises metformin.
- 1 40. The process of claim 30, wherein the glitazone is selected from one or more of
2 pioglitazone, rosiglitazone, troglitazone, ciglitazone and englitazone.
- 1 41. The process of claim 30, wherein the glitazone comprises pioglitazone.
- 1 42. The process of claim 30, wherein after oral administration the biguanide is
2 released over a period of about 4 to about 36 hours.
- 1 43. The process of claim 42, wherein the biguanide is released over a period of about
2 8 to about 24 hours.
- 1 44. The process of claim 30, further comprising forming a tablet or a capsule.
- 1 45. The process of claim 44, further comprising coating the tablet.
- 1 46. The process of claim 44, wherein the capsule contains one or more of pellets,
2 beads, granules, multiparticulates, tablets and powder.

- 1 47. The process of claim 48 wherein the core comprises a matrix.
- 1 48. The process of claim 30, wherein the matrix comprises a uniform mixture of the
2 biguanide and one or more rate controlling polymers.
- 1 49. The process of claim 48, wherein the one or more rate-controlling polymers may
2 be either or both of hydrophilic and hydrophobic.
- 1 50. The process of claim 30, wherein the matrix further comprises one or more
2 pharmaceutically acceptable excipients.
- 1 51. The process of claim 50, wherein the pharmaceutically acceptable excipients
2 comprise one or more of diluents, lubricants, disintegrants, binders, glidants,
3 colorants, and flavorants.
- 1 52. The process of claim 30, wherein the biguanide is layered onto pharmaceutically
2 inert core or seeds.
- 1 53. The process of claim 52, wherein the inert core or seeds are hydrosoluble or
2 hydroinsoluble.
- 1 54. The process of claim 30, wherein the immediate release outer layer further
2 comprises film-forming polymers and optionally other pharmaceutically
3 acceptable excipients.
- 1 55. The process of claim 54, wherein the film-forming polymers comprise water-
2 soluble polymers.
- 1 56. The process of claim 54, wherein the pharmaceutically acceptable excipients
2 comprise one or more of plasticizers, opacifiers and colorants.
- 1 57. The process of claim 30, further comprising placing a seal-coat over the core,
2 wherein the seal-coat comprises hydrophilic polymers.
- 1 58. A process for preparing a bilayered, solid, orally administered pharmaceutical
2 dosage form of a biguanide and a glitazone, the process comprising:

- 3 a. dispersing the biguanide in an extended release carrier base material;
- 4 b. separately dispersing the glitazone in an immediate release carrier base
- 5 material; and
- 6 c. compressing the material of step a and step b to form bilayered tablet.

1 59. The process of claim 58, wherein the immediate release carrier base material
2 further comprises one or more wetting agents before or after dispersing the
3 glitazone.

1 60. The process of claim 59, wherein the glitazone and the one or more wetting
2 agents are present in a weight ratio ranging from about 10:1 to about 1:25.

1 61. The process of claim 59, wherein the one or more wetting agents are selected
2 from amongst hydrophilic or hydrophobic surfactants.

1 62. The process of claim 61, wherein the hydrophilic surfactants are selected from
2 one or more of non-ionic surfactants, ionic surfactants or mixtures thereof.

1 63. The process of claim 61, wherein the hydrophobic surfactants are selected from
2 one or more of alcohols; polyoxyethylene alkylethers; fatty acids; glycerol fatty
3 acid monoesters; glycerol fatty acid diesters; acetylated glycerol fatty acid
4 monoesters; acetylated glycerol fatty acid diesters, lower alcohol fatty acid esters;
5 polyethylene glycol fatty acid esters; polyethylene glycol glycerol fatty acid
6 esters; polypropylene glycol fatty acid esters; polyoxyethylene glycerides; lactic
7 acid derivatives of monoglycerides; lactic acid derivatives of diglycerides;
8 propylene glycol diglycerides; sorbitan fatty acid esters; polyoxyethylene sorbitan
9 fatty acid esters; polyoxyethylene-polyoxypolypropylene block copolymers,
10 polyethyleneglycols as esters or ethers, polyethoxylated castor oil;
11 polyethoxylated hydrogenated castor oil, polyethoxylated fatty acid from castor
12 oil or polyethoxylated fatty acid from castor oil or polyethoxylated fatty acid from
13 hydrogenated castor oil.

1 64. The process of claim 62, wherein the non-ionic surfactants are selected from the
2 one or more of alkylglucosides; alkylmaltosides; alkylthioglucosides; lauryl

3 macrogolglycerides; caprylocaproyl macrogolglycerides, polyoxyethylene alkyl
4 ethers; polyoxyethylene alkylphenols; polyethylene glycol fatty acid esters;
5 polyethylene glycol glycerol fatty acid esters; polyoxyethylene sorbitan fatty acid
6 esters; polyoxyethylene-polyoxypolypropylene block copolymers; polyglycerol fatty
7 acid esters; polyoxyethylene glycerides; polyoxyethylene sterols, derivatives, and
8 analogues thereof; polyoxyethylene vegetable oils; polyoxyethylene hydrogenated
9 vegetable oils; reaction products of polyols and at least one member of the group
10 consisting of fatty acids, glycerides, vegetable oils, hydrogenated vegetable oils,
11 and sterols; sugar esters, sugar ethers; sucroglycerides; and mixtures thereof.

- 1 65. The process of claim 62, wherein the ionic surfactants are selected from one or
2 more of alkyl ammonium salts; bile acids and salts, analogues, and derivatives
3 thereof; fatty acid derivatives of amino acids, oligopeptides, and polypeptides;
4 glyceride derivatives of amino acids, oligopeptides, and polypeptides; acyl
5 lactylates; monoacetylated tartaric acid esters of monoglycerides, monoacetylated
6 tartaric acid esters of diglycerides, diacetylated tartaric acid esters of
7 monoglycerides, diacetylated tartaric acid esters of diglycerides; succinylated
8 monoglycerides; citric acid esters of monoglycerides; citric acid esters of
9 diglycerides; alginate salts; propylene glycol alginate; lecithins and hydrogenated
10 lecithins; lysolecithin and hydrogenated lysolecithins; lysophospholipids and
11 derivatives thereof; phospholipids and derivatives thereof; salts of alkylsulfates;
12 salts of fatty acids; sodium docusate; and mixtures thereof.
- 1 66. The process of claim 58, wherein the biguanide is selected from one or more of
2 metformin, phenformin and buformin.
- 1 67. The process of claim 58, wherein the biguanide comprises metformin.
- 1 68. The process of claim 58, wherein the glitazone is selected from one or more of
2 pioglitazone, rosiglitazone, troglitazone, ciglitazone and englitazone.
- 1 69. The process of claim 58, wherein the glitazone comprises pioglitazone.

- 1 70. The process of claim 58, wherein after oral administration the biguanide is
2 released over a period of about 4 to about 36 hours.
- 1 71. The process of claim 70, wherein the biguanide is released over a period of about
2 8 to about 24 hours.
- 1 72. The process of claim 58, further comprising forming a tablet or a capsule.
- 1 73. The process of claim 72, further comprising coating the tablet.
- 1 74. The process of claim 72, wherein the capsule contains one or more of pellets,
2 beads, granules, multiparticulates, tablets and powder.
- 1 75. The process of claim 58, wherein the biguanide layer comprises a matrix.
- 1 76. The process of claim 75, wherein the matrix comprises a uniform mixture of the
2 biguanide and one or more rate controlling polymers.
- 1 77. The process of claim 76, wherein the one or more rate-controlling polymers may
2 be either or both of hydrophilic and hydrophobic.
- 1 78. The process of claim 75, wherein the matrix further comprises one or more
2 pharmaceutically acceptable excipients.
- 1 79. The process of claim 78, wherein the pharmaceutically acceptable excipients
2 comprise one or more of diluents, lubricants, disintegrants, binders, glidants,
3 colorants, and flavorants.
- 1 80. The process of claim 58, wherein the biguanide is layered onto pharmaceutically
2 inert core or seeds.
- 1 81. The process of claim 80, wherein the inert core or seeds are hydrosoluble or
2 hydroinsoluble.

- 1 82. The process of claim 58, wherein the immediate release carrier base material
2 further comprises film-forming polymers and optionally other pharmaceutically
3 acceptable excipients.
- 1 83. The process of claim 82, wherein the film-forming polymers comprise water-soluble polymers.
- 1 84. The process of claim 82, wherein the pharmaceutically acceptable excipients
2 comprise one or more of plasticizers, opacifiers and colorants.
- 1 85. The process of claim 58, further comprising providing a seal-coat of one or more
2 hydrophilic polymers between the two layers.
- 1 86. A method of treating non-insulin dependent diabetes mellitus in a patient in need
2 thereof, the method comprising administering a solid, pharmaceutical dosage
3 form of the combination of a biguanide and a glitazone, wherein the dosage form
4 provides an extended-release of the biguanide and an immediate release of the
5 glitazone.
- 1 87. The method of claim 86, wherein the biguanide comprises one or more of
2 metformin, phenformin, and buformin.
- 1 88. The method of claim 86, wherein the biguanide is metformin.
- 1 89. The method of claim 86, wherein the glitazone comprises one or more of
2 pioglitazone, rosiglitazone, troglitazone, ciglitazone and englitazone.
- 1 90. The method of claim 86 wherein the glitazone is pioglitazone.
- 1 91. The method of claim 86, wherein after oral administration the biguanide is
2 released over a period of about 4 to about 36 hours.
- 1 92. The method of claim 86, wherein the biguanide is released over a period of about
2 8 to about 24 hours.
- 1 93. The method of claim 86, wherein the dosage form comprises tablets or capsules.

1 94. The method of claim 86, wherein the dosage form further comprises one or more
2 of sulfonylurea, insulin, alpha-glucosidase inhibitors, meglitinides, fibrates,
3 statins, squalene synthesis inhibitors and angiotensin-converting enzyme
4 inhibitors.

INTERNATIONAL SEARCH REPORT

Internat	pplication No
PCT/IB 03/05140	

A. CLASSIFICATION OF SUBJECT MATTER
 IPC 7 A61K31/425- A61K31/427 A61K9/20

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
 IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	US 2003/187074 A1 (J.HUSSAIN ET AL.) 2 October 2003 (2003-10-02) claims example 4 column 4, paragraphs 38-42 page 5, paragraph 45 page 5, paragraph 55 page 5, paragraph 57 page 6, paragraphs 60-64 page 5, paragraph 47	1-5, 8-15, 18-20, 28-30, 38-41, 44-51, 54-58, 66-69, 72-79, 82-90, 93,94

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the International filing date
- *L* document which may throw doubts on priority, claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the International filing date but later than the priority date claimed

- *T* later document published after the International filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *g* document member of the same patent family

Date of the actual completion of the International search

18 February 2004

Date of mailing of the International search report

04/03/2004

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Scarpioni, U

INTERNATIONAL SEARCH REPORT

International Application No.
PCT/IB 03/05140

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 01 82904 A (AEROPHARM) 8 November 2001 (2001-11-08) cited in the application claims ---	1-94
A	WO 01 82867 A (AEROPHARM) 8 November 2001 (2001-11-08) claims ---	1-94
A	WO 01 82875 A (AEROPHARM) 8 November 2001 (2001-11-08) cited in the application claims ---	1-94
A	US 6 166 043 A (H. IKEDA ET AL.) 26 December 2000 (2000-12-26) cited in the application claims examples ---	1-94

INTERNATIONAL SEARCH REPORT

Inten

al application No.
PCT/IB 03/05140**Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 86-94 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- The additional search fees were accompanied by the applicant's protest.
- No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT
Information on patent family members

International PCT/IB	Application No 03/05140
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

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